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(54) Title: SHAPED PRODUCTS OR STRUCTURES FOR MEDICAL OR RELATED PURPOSES

(57) Abstract

A shaped product or structure, including a prosthetic or implant device, for medical or related purposes is characterised in that it is formed from coral.

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## "SHAPED PRODUCTS OR STRUCTURES FOR MEDICAL OR RELATED PURPOSES"

### **FIELD OF THE INVENTION**

This invention relates to shaped products or structures, including prosthetic or implant devices, for medical or related purposes, and in particular to prosthetic or 5 implant devices and other shaped products or structures for use in bone tissue engineering in the fields of human medicine and dentistry, as well as in non-human veterinary fields.

### **10 BACKGROUND OF THE INVENTION**

Crane *et al.* (1995) point out that skeletal deficiencies resulting from trauma, tumours or abnormal development frequently require surgical intervention to restore normal tissue function. Even though current surgical treatments are often successful, 15 all have associated problems with limitations. The limited supply of autograft tissue and the potential of pathogen transfer with allografts have inspired surgeons and engineers to search for other methods to repair skeletal defects. Synthetic materials such as metals and bone cements have also been used for many years, but often result in stress-shielding to the surrounding bone and fatigue failure of the implant.

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These authors also point out that recent strategies to engineer bone have focused on the use of natural or synthetic materials as scaffolds for cell transplantation or as conduits to guide new bone growth. The success of the strategy is highly

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dependent on the properties of the material, requiring minimally that it be biocompatible, osteoconductive, easily sterilized and degradable over an appropriate time-scale into products that can be metabolized or excreted. In addition, scaffolds for cell transplantation must have a high porosity for maximal cell loading, surface 5 characteristics that support cell growth and differentiated function and appropriate pore morphology for bone tissue ingrowth *in vivo*. The success of conduits relies on their ability to induce surrounding tissue to invade, grow and replace the implanted material.

A variety of materials are under consideration for use as scaffolds or conduits 10 in accordance with these strategies, however there remains a need for new biomaterial that will interact with living bone tissue and modulate bone formation and repair.

In US Patent No. 3,929,971 (Research Corporation) there is disclosed a synthetic biomaterial having a microstructure substantially corresponding to the 15 microstructure of porous carbonate skeletal material of marine life and made up of hydroxyapatite or whitlockite. This synthetic material is made by converting porous carbonate skeletal material of marine life into a phosphate skeletal material possessing a microstructure substantially the same as or corresponding to the microstructure of the carbonate skeletal source material by subjecting the carbonate skeletal material 20 to hydrothermal chemical exchange with a phosphate.

US Patent No. 4,861,733 (Interpore International) discloses calcium phosphate materials useful as bone substitution material or for the manufacture of prosthetic devices which have been prepared from calcium hydroxyapatite material which has a 25 uniformly permeable microporous structure characterised by a substantially uniform pore volume in the range from about 10 to about 90% and by a pronounced three-dimensional fenestrate structure corresponding to the microstructure of the porous carbonate echinoderm or scleractinian coral skeletal material of marine life, by reacting the calcium hydroxyapatite material which has a calcium to phosphorous atomic ratio 30 of about 1.66 with a phosphate-contributing or phosphorous-contributing moiety or with

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a calcium-contributing or calcium oxide-contributing moiety so as to alter the calcium to phosphorous Ca/P atomic ratio to yield a calcium phosphate material retaining the above-described microstructure of the porous carbonate echinoderm or scleractinian coral skeletal material but having a calcium to phosphorous Ca/P atomic ratio less than 5 or greater than 1.6.

Related US Patent No. 4,976,736 (Interpore International) discloses synthetic biomaterials useful for orthopedic dental applications which have a base portion of calcium carbonate and a surface layer of a synthetic phosphate such as 10 hydroxyapatite. The base portion may be a calcium carbonate structure having three-dimensional interconnected porosity such as may be found in porous skeletal carbonate of marine life, e.g. coral porites skeletal aragonite, or it may be porous or non-porous granules of calcium carbonate.

## 15 SUMMARY OF THE INVENTION

According to one aspect of the present invention, there is provided a shaped product or structure for medical or related purposes, characterised in that it is formed from coral, preferably coral of the species *Porites* or *Acropora* species, particularly 20 *Acropora* species such as *Acropora grandis*.

In this aspect, the present invention also provides a device for medical or related purposes which comprises an assembly of shaped products or structures, as broadly described above.

25

According to another aspect of invention, there is provided a prosthetic or implant device for medical or related purposes, particularly for use in repair of fracture of a long bone or when elongation of a long bone is required. The prosthetic or implant device of this aspect of the invention comprises an assembly of shaped members 30 formed from coral, preferably coral of the species *Porites* or *Acropora*, the assembly

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comprising first and second elongate members each of which is adapted to be fixed at one end to a long bone, the other ends of each of said first and second elongate members being externally and internally threaded, respectively, so that said first member is received by said second member in a threaded inter-engagement to enable  
5 the overall length of the device to be adjusted.

The threaded inter-engagement of the first and second elongate members of the device of this invention enables the overall length of the device to be adjusted to the length required for the particular use, that is in repair of a fracture or in elongation  
10 of a long bone, before the device is fixed in place, for example between the ends of a fractured long bone.

Preferably, an internally-threaded third member is also provided in threaded engagement with the first member to act as a locking nut and lock the second member  
15 with respect to the first member at a desired overall length.

Throughout this specification, unless the context requires, the word "comprise" or variations such as "comprises" or "comprising" will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other  
20 integer or group of integers.

## DETAILED DESCRIPTION OF THE INVENTION

Coral is the hard deposit consisting principally of calcium carbonate which is  
25 built up by minute colonial marine invertebrate animals called coral polyps . The corals of the order *Hydrocoralline* of the Class *Hydrozoa* exist as sessile colonies with a massive encrusting or branching exoskeleton with pits in the surface from which the polyps arise.

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The corals of the orders *Alcyonaria* and *Zoantharia* of the Class Anthozoa (Actinozoa) are of different form and habits. Those of the alcyonarians are made up of minute spicules formed within the tissues, occasionally compacted in a hard central rod running through the entire colony and sometimes supplemented by an external covering. Zoantharian corals build up hard deposits externally beneath the basal disk which attaches them to the ocean floor. As new individuals arise from the edge of the living tissue their deposits become continuous with those already laid down and so large colonies produce extensive masses of coral rock. The form of these deposits varies. Some are slender and branching and others rounded and massive. They have received common names such as staghorn coral and brain coral (Van Nostrand's Scientific Encyclopaedia, Eight Edition, Van Nostrand, Reinhold, 1995).

Surgical repair of large cortical and other defects, in both humans and non-humans, resulting from traumas or tumour resection presents many challenges. Significant morbidity is associated with autograft harvest sites and the quantity of material available for use in the repair is limited. A bone defect might regenerate more efficiently if a stromal substitute is implanted to provide a framework for organisation of the osteons. By providing a scaffold containing spaces morphologically compatible with osteons and their vascular interconnections, an association between biocomponents and biologic regenerative and repair responses can be promoted.

Each year, a large number of cases involved with bone fractures and deficiencies result in mechanical fixation using temporary or permanent hardware. The use of natural and biodegradable materials for surgical applications can provide strong, biocompatible and degradable hardware that can be manufactured with low cost and may consequently reduce the need for a second surgical intervention following the healing process. It also can be custom fabricated according to special needs. High risk, elderly patients may represent a particular challenge since increasing the need of a second surgical intervention and hospitalization time is crucial. There is a growing

search for biocompatible and biodegradable materials for use as hardware for surgical applications.

A wide range of metallic, ceramic, polymeric and composite materials have  
5 been used in the construction of medical devices for implantation into the human body  
(Hench and Wilson, 1993). The types of implant can be presented as follows: (1)  
nearly inert; (2) porous; (3) bioactive; (4) resorbable. Porous structure devices were  
developed to prevent loosening of the implants. When the porous implant is metal, the  
large interfacial area can provide a focus for corrosion of the implant and loss of metal  
10 ions into the tissue. A film of hydroxyapatite (HA) often coats these, for a more rapid  
bond of the natural bone to the devices (Hench and Wilson, 1993; Lacefield, 1993;  
Dunn and Maxiian, 1994). The coatings, however, often dissolve with time, which  
limits their effectiveness. In porous implants, it is necessary for the pores to be at least  
100 micrometers in diameter to allow capillaries to provide a blood supply to the  
15 ingrown connective tissue. It is important to note that interfacial stability is crucial for  
a clinical successful implantation. Resorbable implants are designed to gradually  
degrade and be replaced with natural tissue, leading to regeneration of tissue instead  
of its replacement. The difficulty is to meet the requirements of strength and short-term  
and mechanical performance during the processes.

20

Carbonate skeletons of coral polyp and other reef-building organisms possess  
a unique microporous lattice structure. This lattice structure promotes ingrowth of  
connective tissue and eventual bone deposition within the scaffold. Each species of  
organism governs the microstructural properties of its skeleton to a high degree,  
25 however the morphological parameters used to describe the colonies taxonomically  
do not suffice to characterise them from a materials standpoint. The rationale for using  
the calcium carbonate structure of coral as a bone substitute material is based on the  
fact that natural bone is approximately 70% hydroxyapatite by weight and 50% by  
volume. Porosity and interconnectivity are key factors with respect to the amount and  
30 type of ingrowth of tissue into the lattice structure of coral. For example, in highly

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porous and interconnected implants, tissue ingrowth starts by day three or four. By four weeks, the ingrowth is completed and apposition of bone covering the pore walls has began. In animal models, bone ingrowth may be nearly complete by three months.

5

The study of coral as an osseous substitute began as early as 1970s in France and USA. It reflects different ideas and approaches, the first human graft was carried out in 1979 (Patel *et al.*, 1980). One of the early approaches by American researchers was to replicate the porous calcium carbonate skeletal structure of some marine 10 organisms (White *et al.*, 1972). They replicated the microstructure in ceramic, metal, and polymer prosthetic materials in a process that they termed replamineform (White *et al.*, 1972). In another process, using hydrothermal exchange, coral skeletal carbonate was converted to calcium phosphate (Roy and Linnehan, 1974). The result was a compound with good biocompatibility and hardness, its derivatives are still a 15 common material in bone grafting. There is however a continuous debate (Holmes, 1979; Shors and Holmes, 1993; Marchac and Sandor, 1994; Ripamonti, 1996), over the properties of the converted material. It is argued that the conversion process may cause the coral to lose some of its unique properties that are characterised by its architectural configuration and integration into bone tissue. Both natural and converted 20 coral have undergone some clinical trials and are currently available. Coralline and coralline derivative implants are also under experimental study using animal models (e.g. Glass, 1989; Brain *et al.*, 1993; Ripamonti, 1996) and human clinical trials and evaluation for repair or replacement of broken or diseased bones. Studies are currently being conducted for restoration or replacement of both broken and diseased 25 bone for orthopaedic, cranial, maxillofacial, dental and ocular and orbital floor implants (e.g. Holmes, 1993; Papacharalambous, 1993; Bronzino, 1995; Mercier *et al.*, 1996).

It has also been suggested that in some cases of mechanical failure of internal fixation for hip fractures, which is common in elderly patients, replacement of lost bone 30 trabeculae may improve the mechanical strength of fixation (Cirotteau, 1993). Holmes

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(1993) has summarised the main clinical applications for porous hydroxyapatite of marine origin. In most of these cases, solid blocks, rods or granular forms of coralline materials have been used to fill gap and contour defects (Marchac and Sandor, 1994).

5 It has been noted that the main obstacle in the use of hydroxyapatite and porous coralline materials for load-bearing implants is the relatively poor mechanical properties of these materials, mainly low elasticity and high brittleness, and suggested that future development should focus on the optimisation of properties and microstructural components of the material and impregnation with molecular and  
10 cellular agents (Holmes, 1993; Crane *et al.*, 1995; Ashby *et al.*, 1996; Dee and Bizios, 1996).

Particularly preferred for use in the present invention are two species of corals. The first one, *Porites* is more porous and softer; while the other *Acropora* is stronger,  
15 harder and less porous.

### I. *Porites*

The entire skeleton deposited by a single polyp or by a colony is the corallum.  
20 The skeletons around an individual polyp are corallites and the upper open or end of a carollities is the calyx. The calices are mostly arranged in a hexagonal closed packed array. *Porites* species traditionally have been difficult to distinguish. Confusion results from the fact that some coral species tend to be plastic mainly in response to some environmental parameters such as light intensity, water motion, temperature etc.  
25 The plasticity is evidenced by the same species exhibiting a variety of growth forms and colours etc. In most species, the void to solid ratios is generally in the range of 0.4 to 0.6, and the void phase completely interconnects, forming a highly regular network that interpenetrates the solid calcium carbonate phase. In some species, the micro architecture of the solid and void spaces is nearly identical. The species control  
30 regulatory of microstructure characteristics is attractive to material scientists because

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this uniform and interconnecting architecture has not been matched in man-made, synthetic materials.

### Some typical mechanical properties of *Porites* coral

Property	Test	Orientation	Mean	Range
Crush Strength (psi)	Compression	Parallel Perpendicular	1343 626	997-1675 257-963
Ultimate strength (N·cm <sup>-1</sup> )	Compression	Perpendicular	373	251-544
Stiffness (N·cm <sup>-1</sup> )	Compression	Perpendicular	8300	3310-11470
Energy absorption (N·cm)	Compression	Perpendicular	9.9	4.5-13
Tensile strength (gm·cm <sup>-2</sup> × 10 <sup>4</sup> )	4-point bending	Not reported	Not reported	2.4-3.3
Young's modulus (gm·cm <sup>-2</sup> × 10 <sup>4</sup> )	4-point bending	Not reported	Not reported	5.2-6.0
Elastic modulus (dynes - cm <sup>-2</sup> × 10 <sup>10</sup> )	Resonance frequency	Parallel Perpendicular	4.8 2.6	3.6 - 5.8 1.9 - 3.2

Some *Porites* species are highly porous and possess a regular and uniform micro configuration (structure) of the skeleton. Colonies can grow to 10m in diameter and can be found in the reef slopes and lagoons. The average density for *Porites* species from the Great Barrier Reef in Australia is ~1.4 g/cm<sup>3</sup>. The average pore size in species growing at outer edge of the Great Barrier Reef is ~200µ but it can vary between the locations.

## II. *Acropora*

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*Acropora* species grow widely throughout the tropic seas. The most common growth form of *Acropora* is the branched form with *Acropora grandis* forming staghorn-

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like colonies. Branches of a typical colony can be very long (a few metres in height) and as thick as 10-15cm. This species grows 20-25cm a year. Since this species is very common and fast growing, samples can be easily collected in sheltered areas of the coral reefs. In addition it is also very easy to culture this species so that collection from the coral reefs can be avoided by use of cultured coral material.

The average skeletal density of *Acropora grandis* is ~2.7g/cm<sup>3</sup>. Because the skeleton of this coral species is dense and strong, it can be easily machined to a variety of configurations of shaped products or structures of different sizes, for example 10 by grinding. This material is particularly suited for use in an implant device, in particular for load bearing bones where strength is an essential property of the implant device.

As previously described, the prosthetic or implant devices and other shaped 15 products or structures of the present invention are provided for medical or related purposes. The term "medical or related purposes" is used throughout this specification to include the fields of human and non-human medicine and dentistry in particular. Thus the shaped products or structures of this invention may be used as bone implants 20 or prostheses, or as dental implants or prostheses. In other embodiments, the shaped products or structures may be "hardware" items for medical or related purposes including, but not limited to, various cylinders, sleeves, pins, screws, bolts, nuts, spacers, flat or curved plates or the like. Some typical hardware items are shown by way of example only in Figure 1. These shaped products or structures which are "hardware" items are preferably formed from coral of the species *Acropora*.

25

The present invention also extends to devices for medical or related purposes which comprise an assembly of two or more shaped products or structures of this invention. Figure 2 shows a typical such device, however it is to be understood that this Figure is included by way of example only and the present invention is not 30 restricted to devices of the type shown in Figure 2.

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Figure 2 shows an implant device 10 for insertion between the ends 30 and 31 of a long bone (see Fig 2e), for example the ends formed by fracture of the long bone, or when elongation of the bone is needed. Device 10 comprises a threaded male pin 11 (see Fig 2a), an internally threaded female socket 12 (see Fig 2b) and an internally threaded locking nut 13 (see Fig 2c). Fig 2d shows the assembled device 10. As shown in Fig 2a, male pin 11 (which is optionally hollow as shown at 23) consists of an externally threaded shank portion 21 and a head portion 22 which incorporates a socket 24 of suitable dimensions to receive the end of a long bone, which in use of the device will be fixed into the socket, for example using bone cement or similar material or by use of suitable screws, pins or the like. Female socket 12 is internally threaded as shown at 25, and is similarly provided with a socket 26 to receive the end portion of a long bone. Locking nut 13 is also internally threaded as shown at 27. It will be evident from Fig 2d which shows the assembled device 10 that the overall length of the device, and hence the distance between the ends of a long bone into which the device is inserted, can be adjusted by screwing the female socket 12 along the shank portion 21 of the male pin 11, and then locking the socket 12 in place with the locking nut 13. The various shaped members of the device 10 are preferably formed from coral of the species *Porites* or *Acropora*.

In work leading to the present invention, off-shore coral colonies were collected from the Great Barrier Reef in Australia using lifting bags and baskets. The colonies were immediately soaked in a bleaching solution. Since clearing the residual organic matrix is one of the first tasks in the purification process, the first steps were started immediately following collection of the coral. It has been found that by bleaching the colonies immediately after collection and while the colonies were still wet, the best results and cleanest colonies were obtained.

The colonies were then cut into blocks and machined into a variety of configurations as shown by way of example in Figure 1. After the initial bleaching and cleaning processes, samples were oven dried and kept in a semi-sterile, dry

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environment to avoid humidity and bacterial infections of the cleaned skeletal materials.

Special holders were fabricated from soft polyvinyl chloride polymer material to 5 firmly secure the samples to avoid fractures during the machine processing of the samples.

Oven dried samples were transferred into an hydrostatic pressure chamber where distilled water was pressurised (150psi) into the skeleton, and particularly the 10 fine cavities. This process reduces the amount of dust particles produced and allows easier machining (eg. grinding) of the samples. As an alternative, it has been found that dipping samples in liquid nitrogen creates a more solid substrate. After dipping in liquid nitrogen for 2 minutes, processing of the samples was easier and the surface produced by the machine processing was smoother.

15

As noted above, the products or structures may be machined into a variety of configurations for various medical or related purposes, and quite complex shapes such as cylindrical structures and threaded structures may be formed by appropriate machine processing.

20

Finally, the shaped products or structures of the present invention may be used to adsorb or bind, and deliver, other therapeutically active substances which assist in the bone repair or regeneration process, or which have other desired therapeutic activity. Such substances include, by way of example, known synthetic or 25 semisynthetic antibiotics which may be introduced into the pore cavities of the shaped product or structure, or a growth factor such as transforming growth factor or one of the bone morphogenic proteins which can be used to assist or promote bone ingrowth.

Persons skilled in this art will appreciate that variations and modifications may 30 be made to the invention as broadly described herein, other than those specifically

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described without departing from the spirit and scope of the invention. It is to be understood that this invention extends to include all such variations and modifications.

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**CLAIMS:**

1. A shaped product or structure for medical or related purposes, characterised in that it is formed from coral.
2. A product or structure according to claim 1, characterised in that the coral is of the species *Porites*.
3. A product or structure according to claim 1, characterised in that the coral is of the species *Acropora*.
4. A product or structure according to claim 3, characterised in that the coral is *Acropora grandis*.
5. A product or structure according to claim 1 which is a hardware item for medical or related purposes.
6. A product or structure according to claim 5, which is a cylinder, sleeve, pin, screw, bolt, nut, spacer, or flat or curved plate, for medical or related purposes.
7. A product or structure according to claim 1, which is a prosthetic or implant device.
8. A product or structure according to claim 1, wherein a therapeutically active substance is adsorbed or bound onto the coral.
9. A product or structure according to claim 8, wherein the therapeutically active substance is an antibiotic.

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10. A product or structure according to claim 8, wherein the therapeutically active substance is a growth factor to assist or promote bone ingrowth.
11. A device for medical or related purposes which comprises an assembly of shaped products or structures according to any of claims 1 to 10.
12. A device according to claim 8 which is an assembly comprising first and second elongate members each of which is adapted to be fixed at one end to a long bone, the other ends of each of said first and second elongate members being externally and internally threaded, respectively, so that said first member is received by said second member in a threaded inter-engagement to enable the overall length of the device to be adjusted, and optionally an internally-threaded third member in threaded engagement with the first member to act as a locking nut and lock the second member with respect to the first member at a desired overall length.

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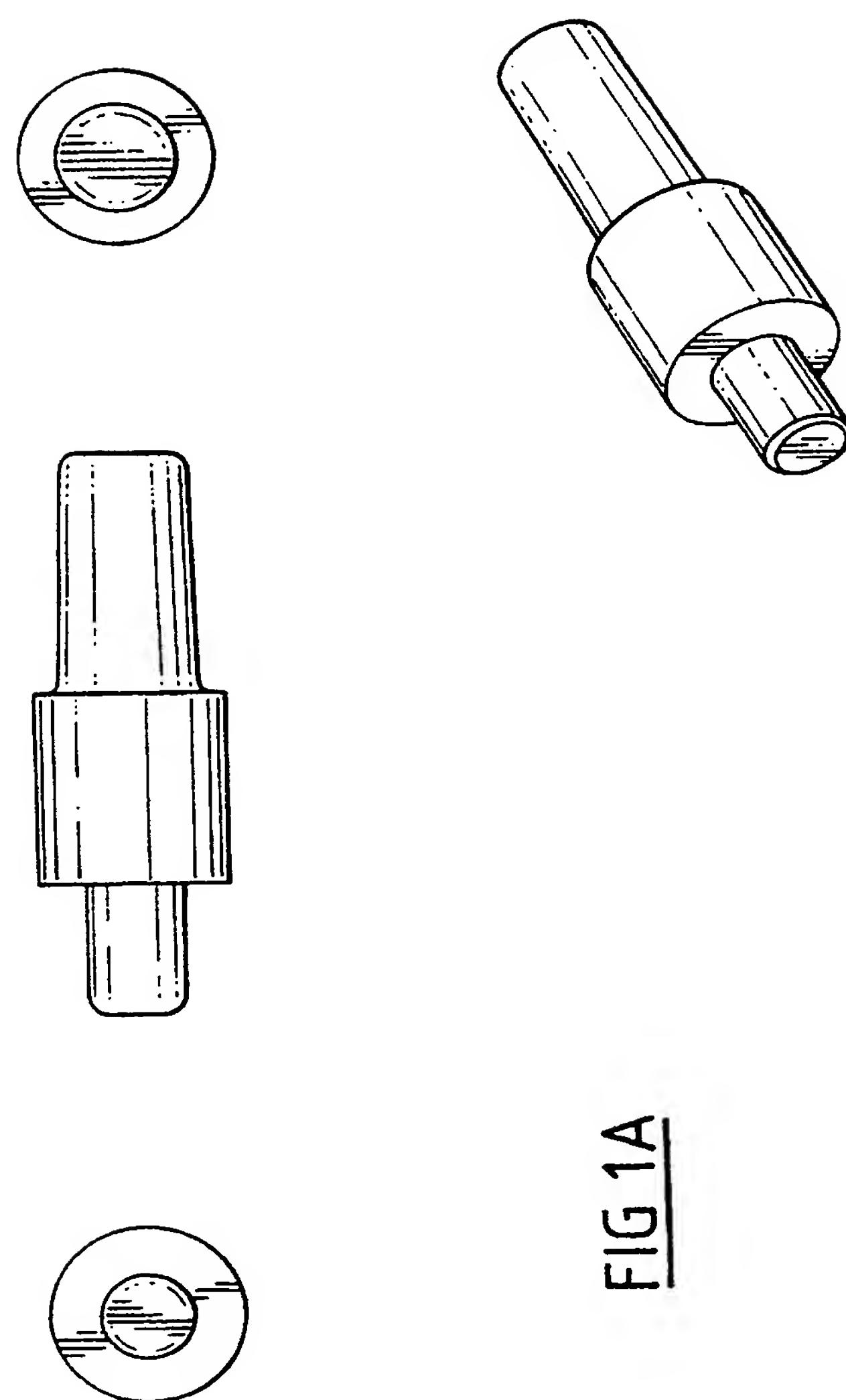


FIG 1A

**SUBSTITUTE SHEET (RULE 26)**

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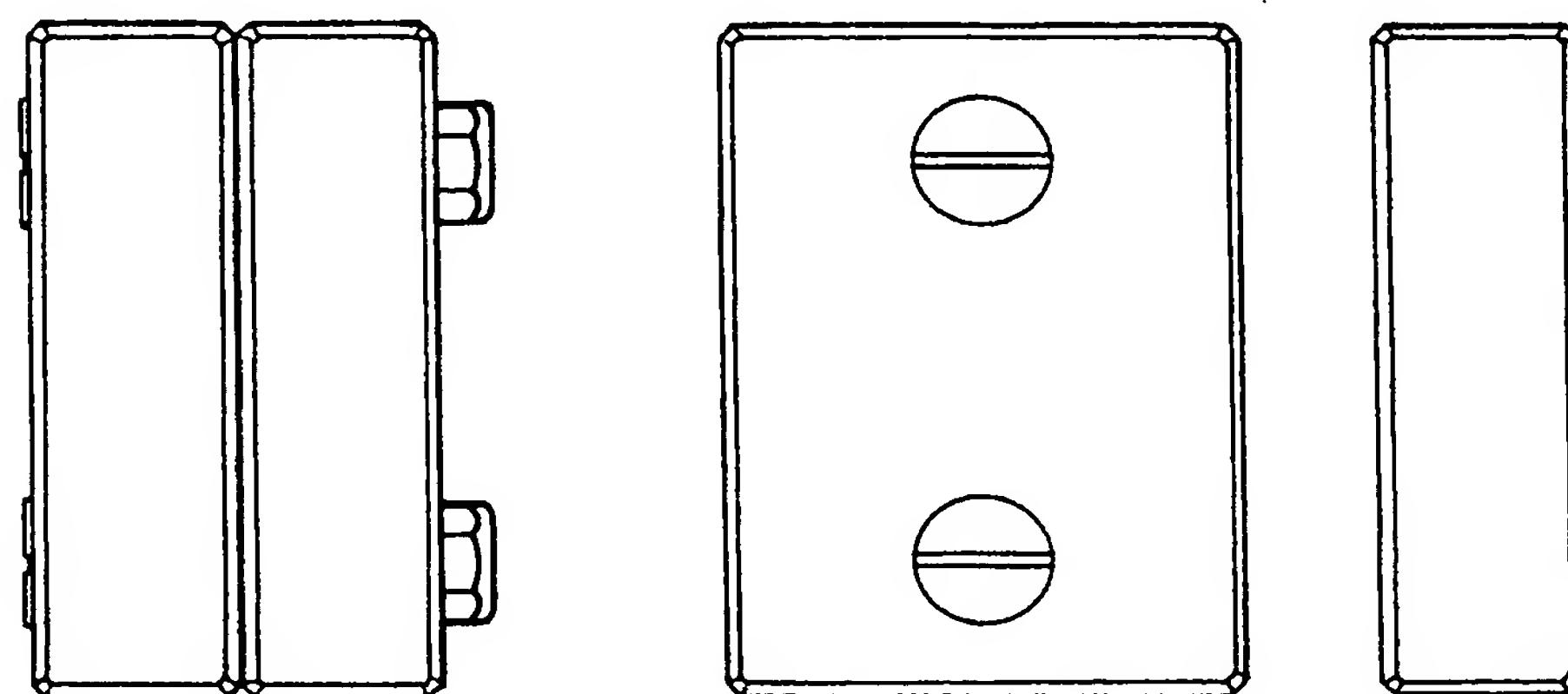
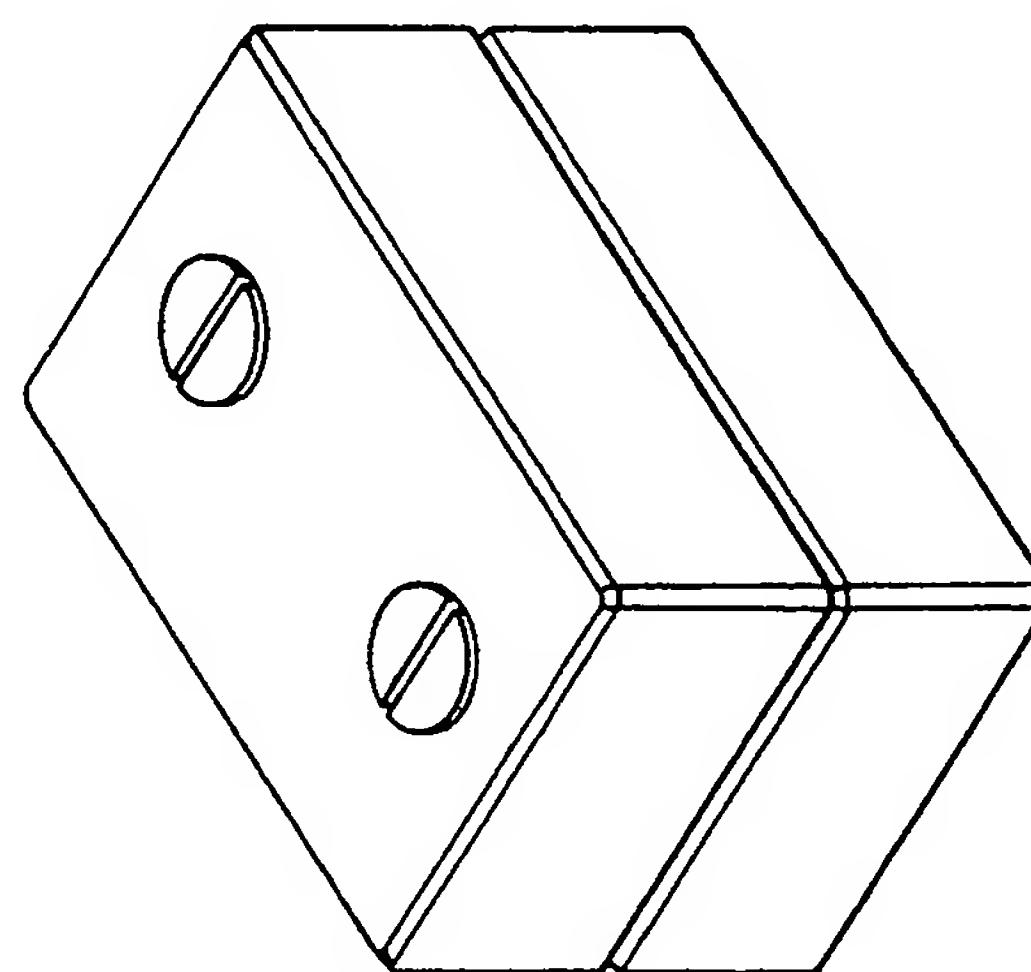
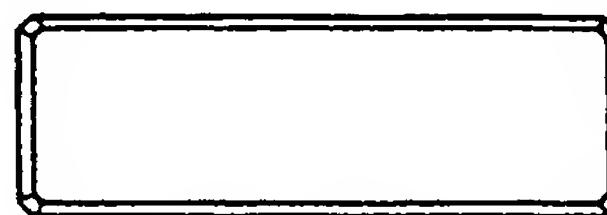


FIG 1B



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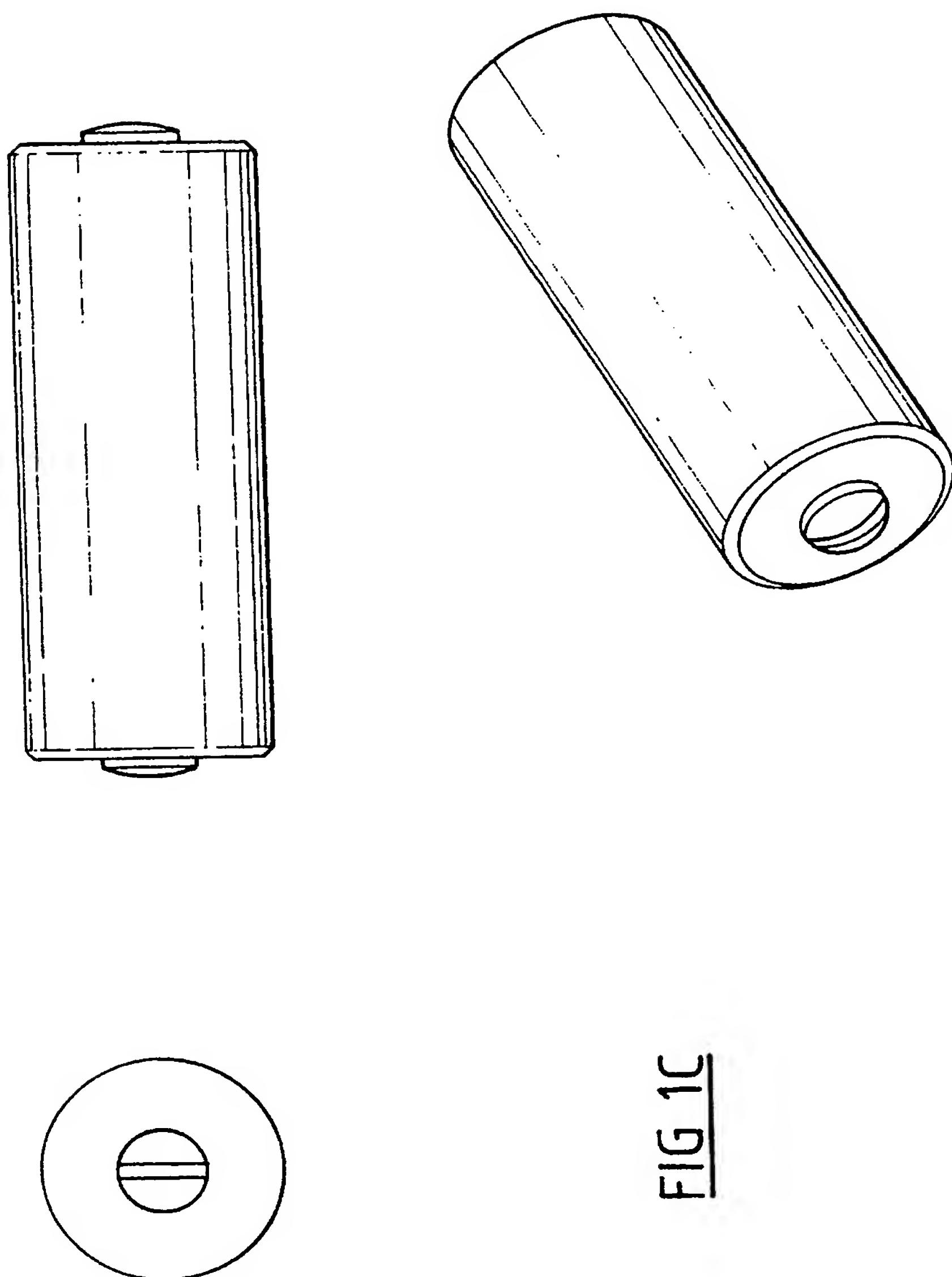


FIG 1C

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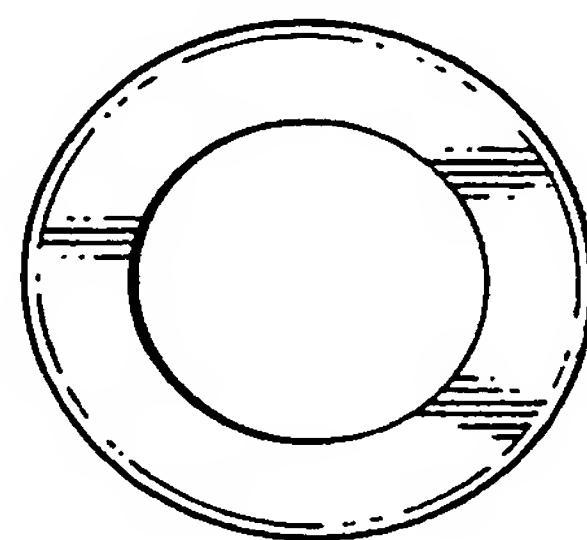
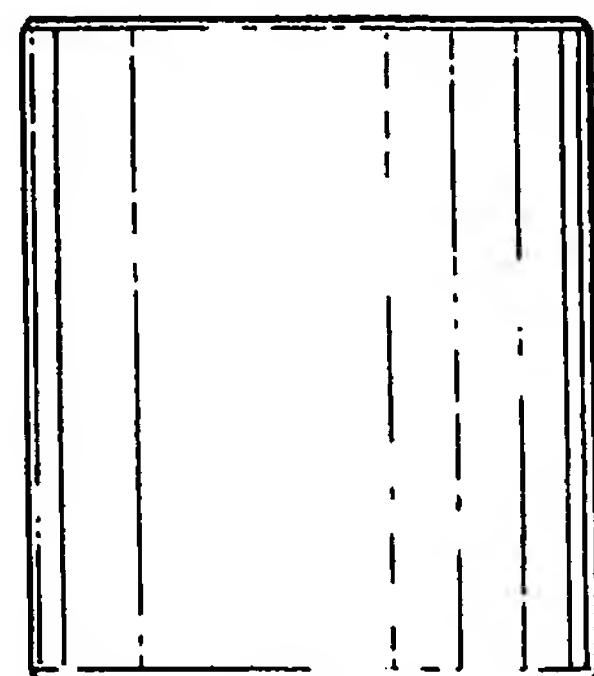
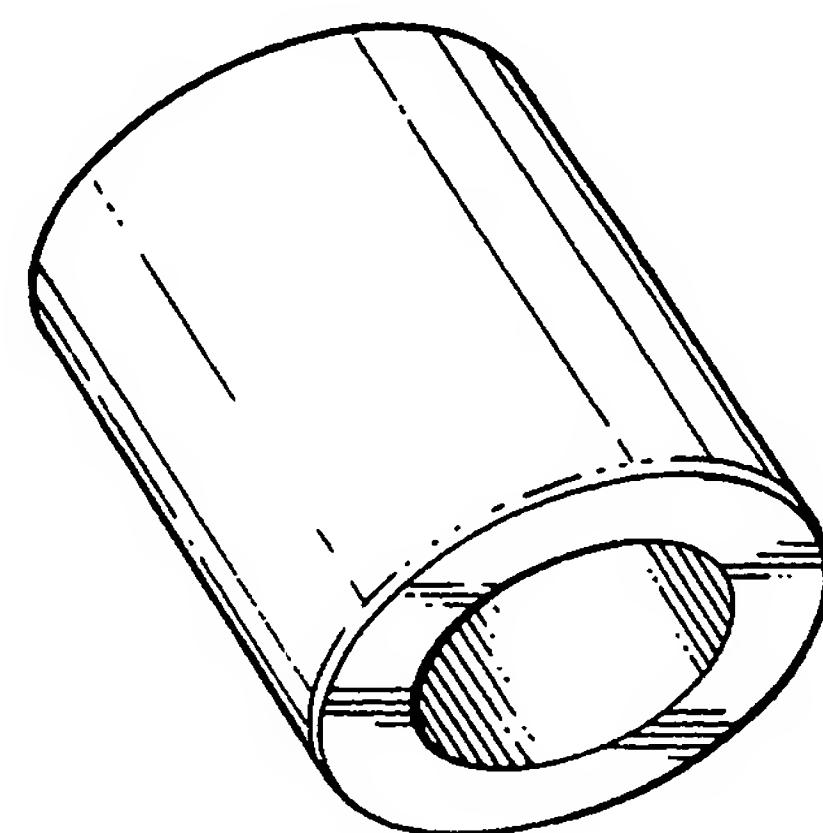


FIG 1D

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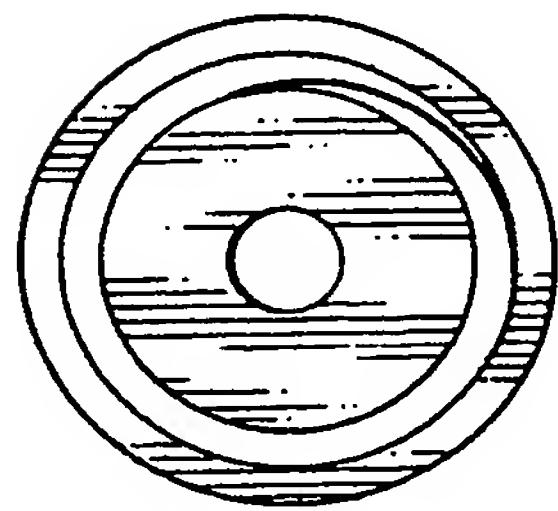
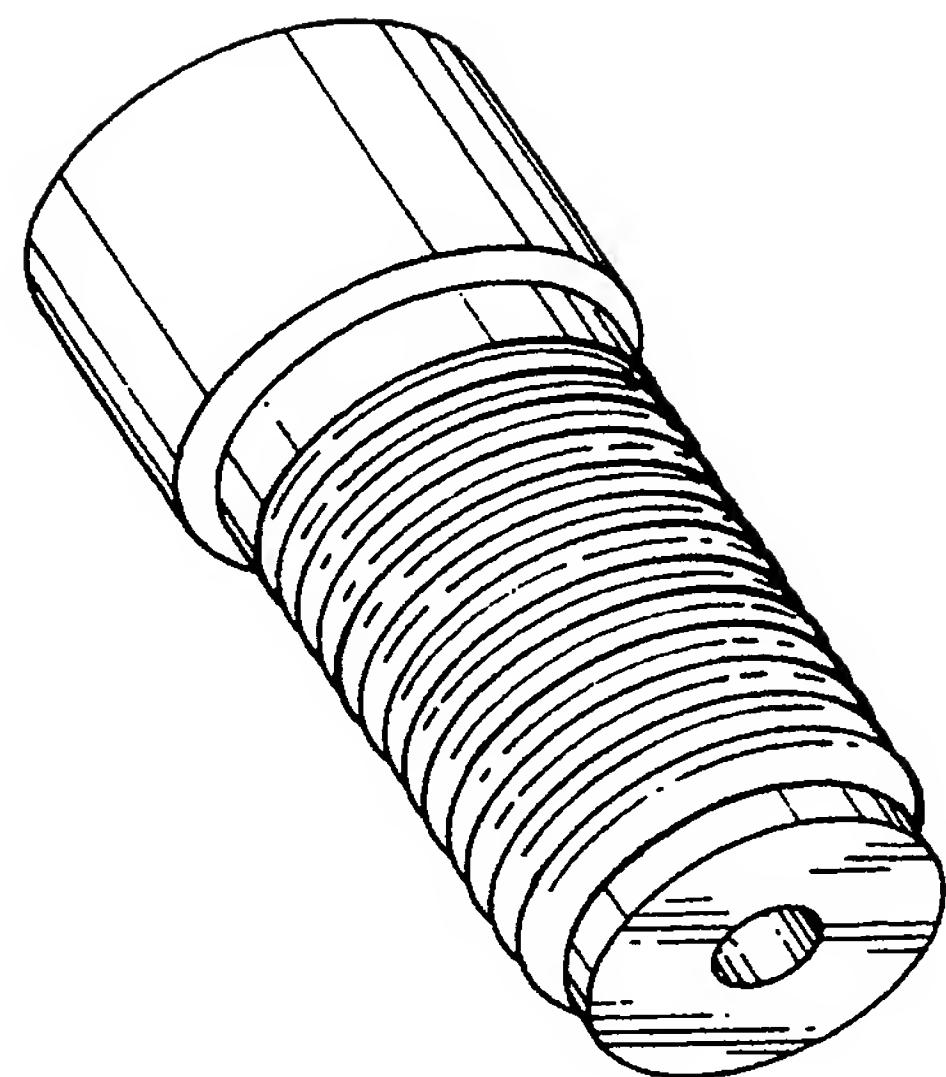
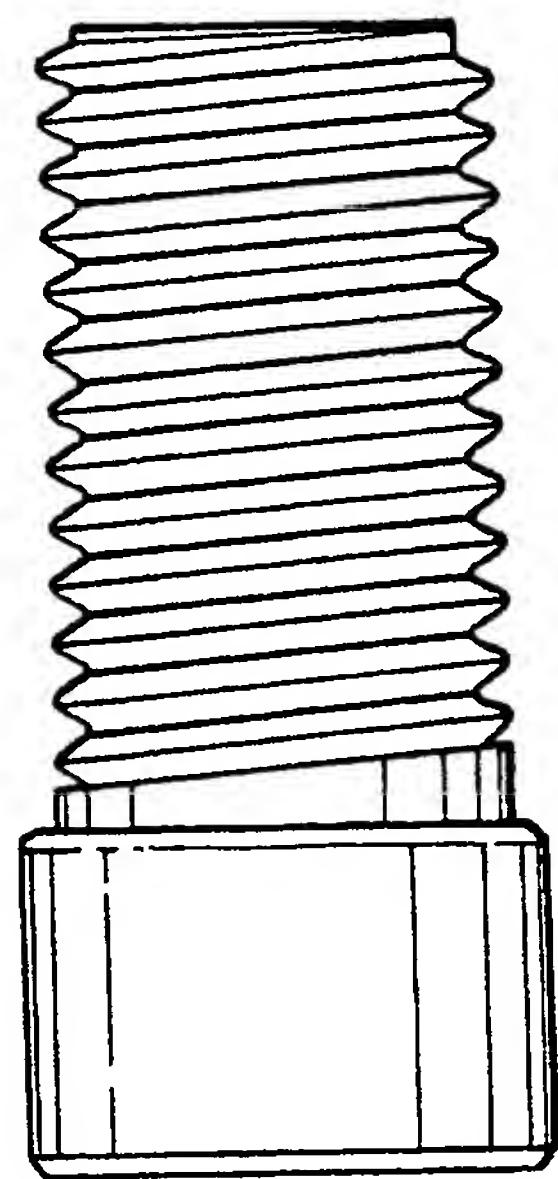
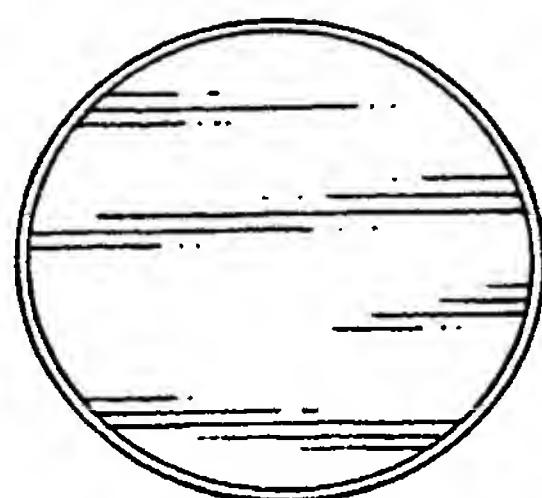
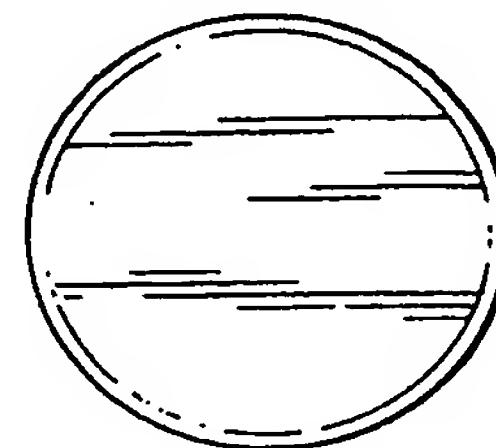
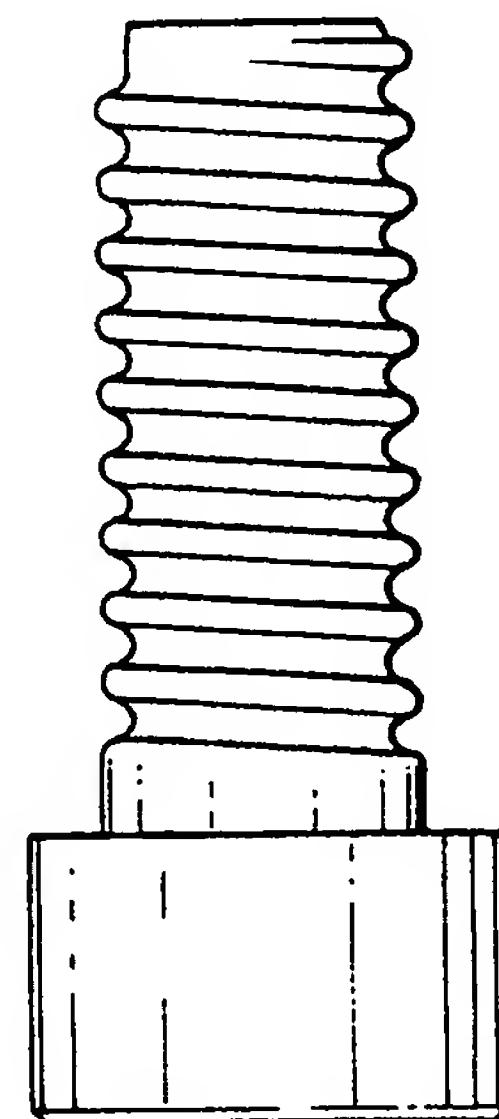
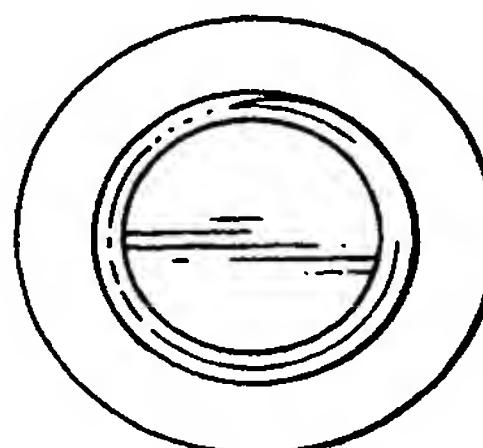
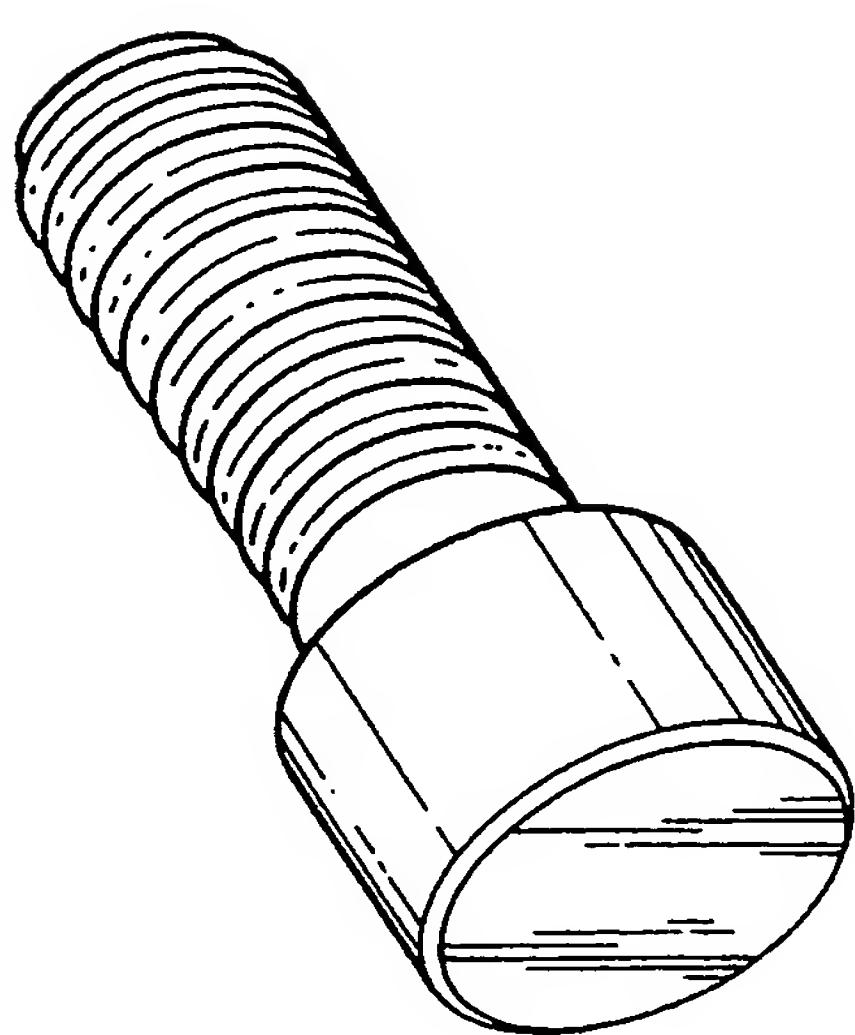


FIG 1E

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FIG 1F



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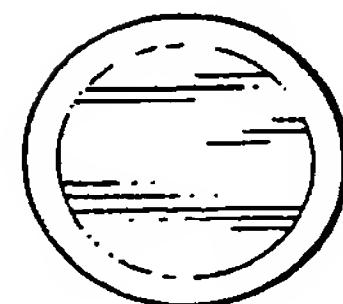
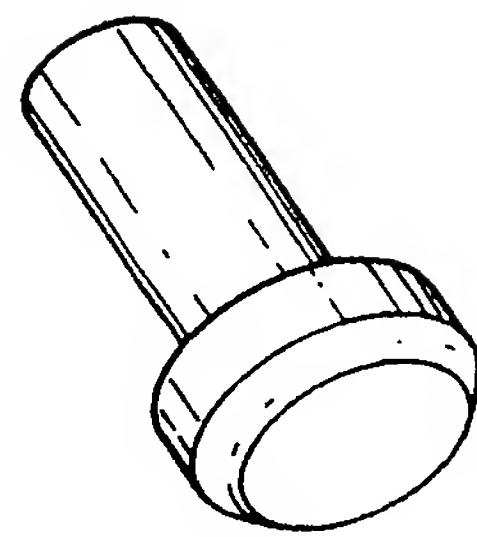
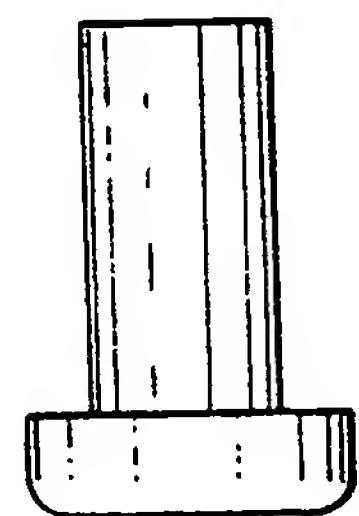
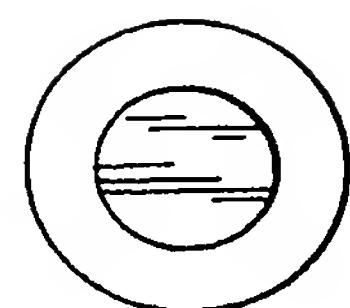
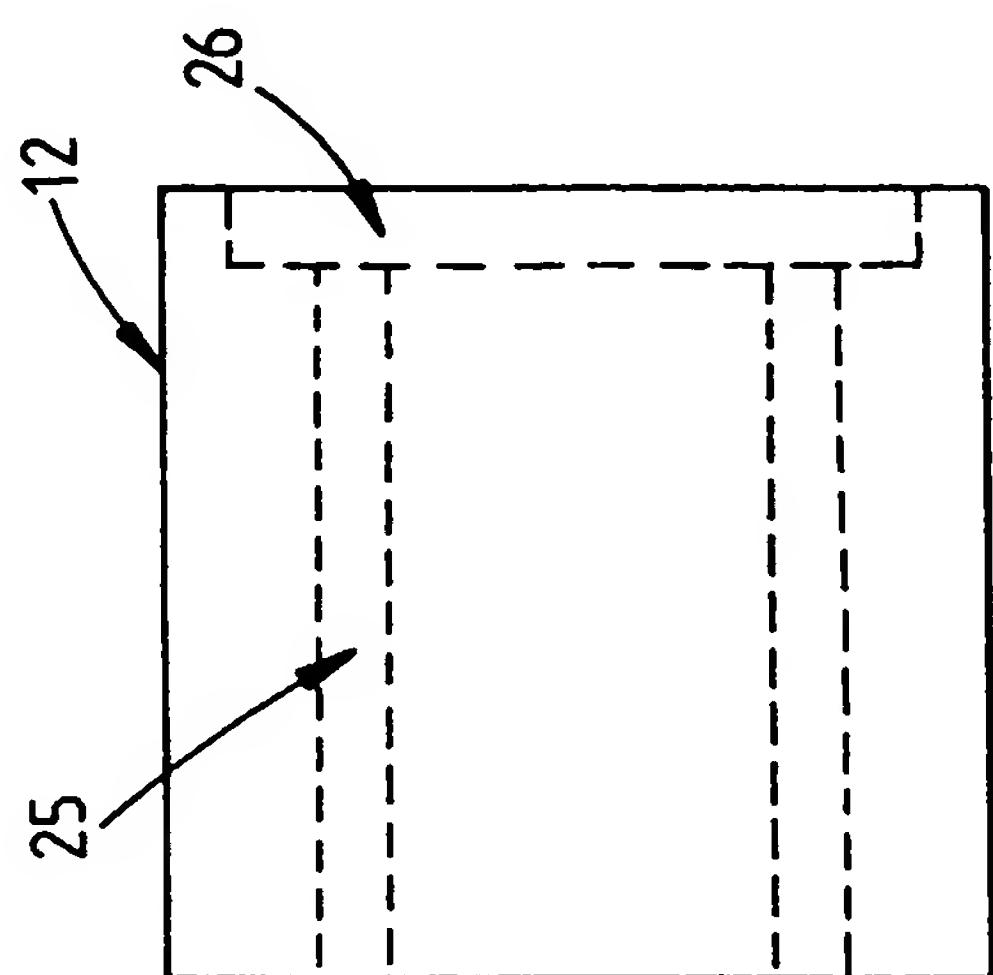
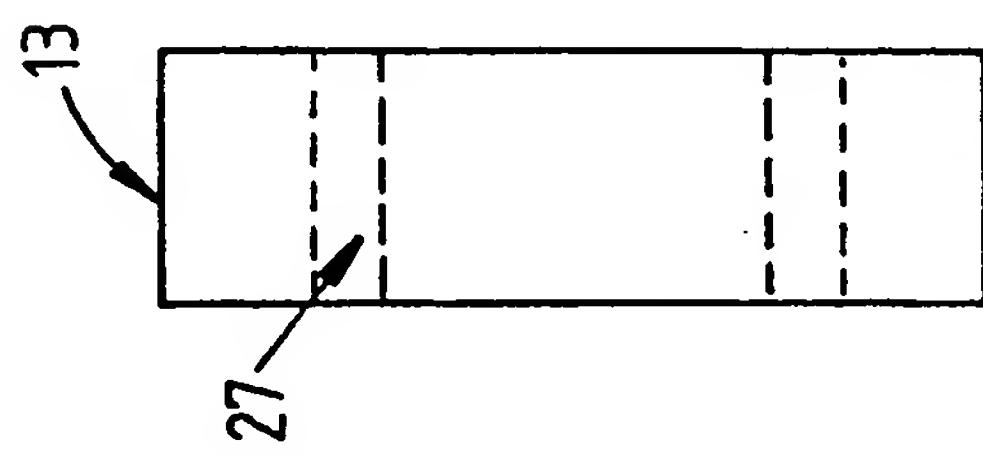
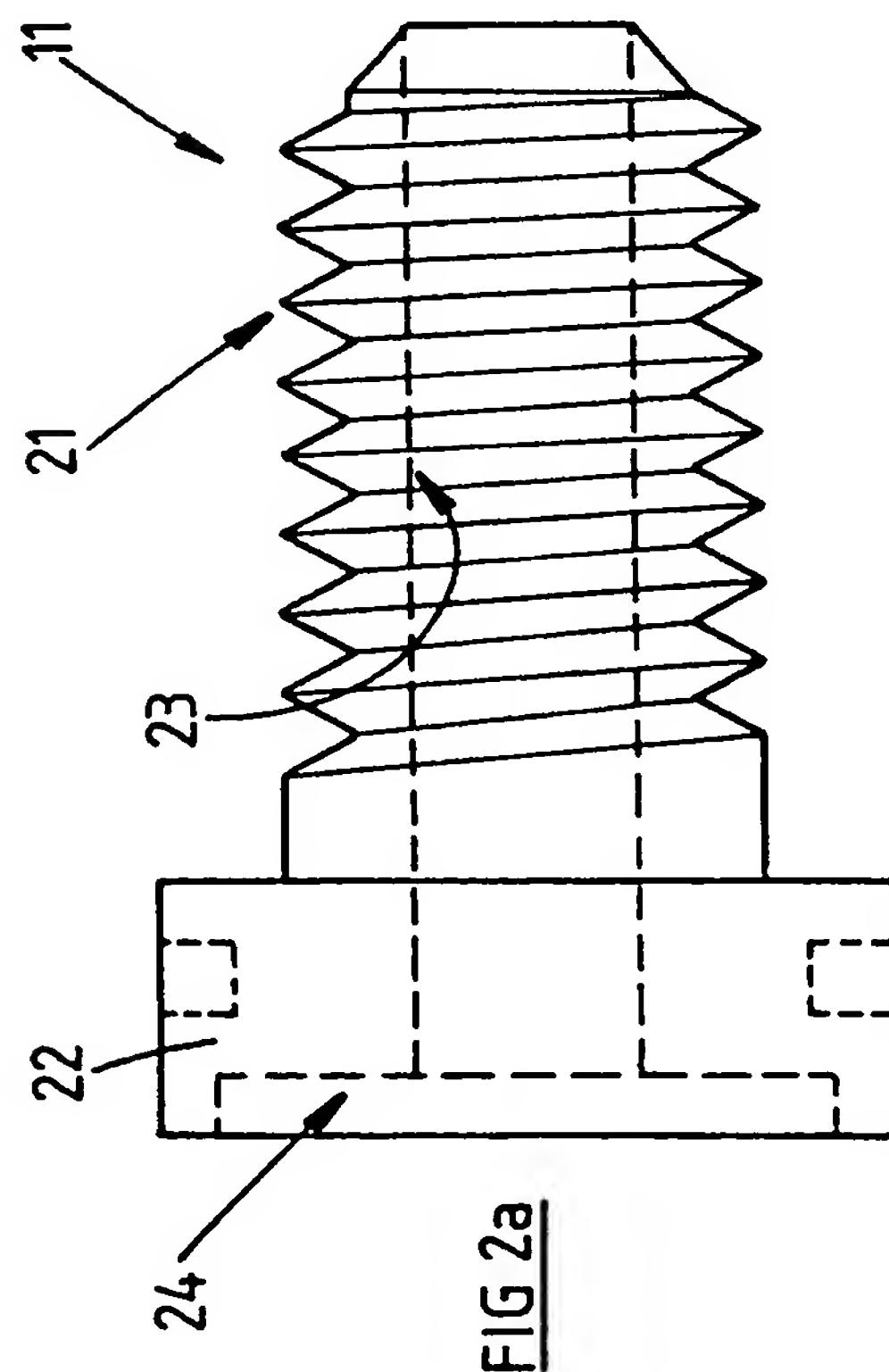
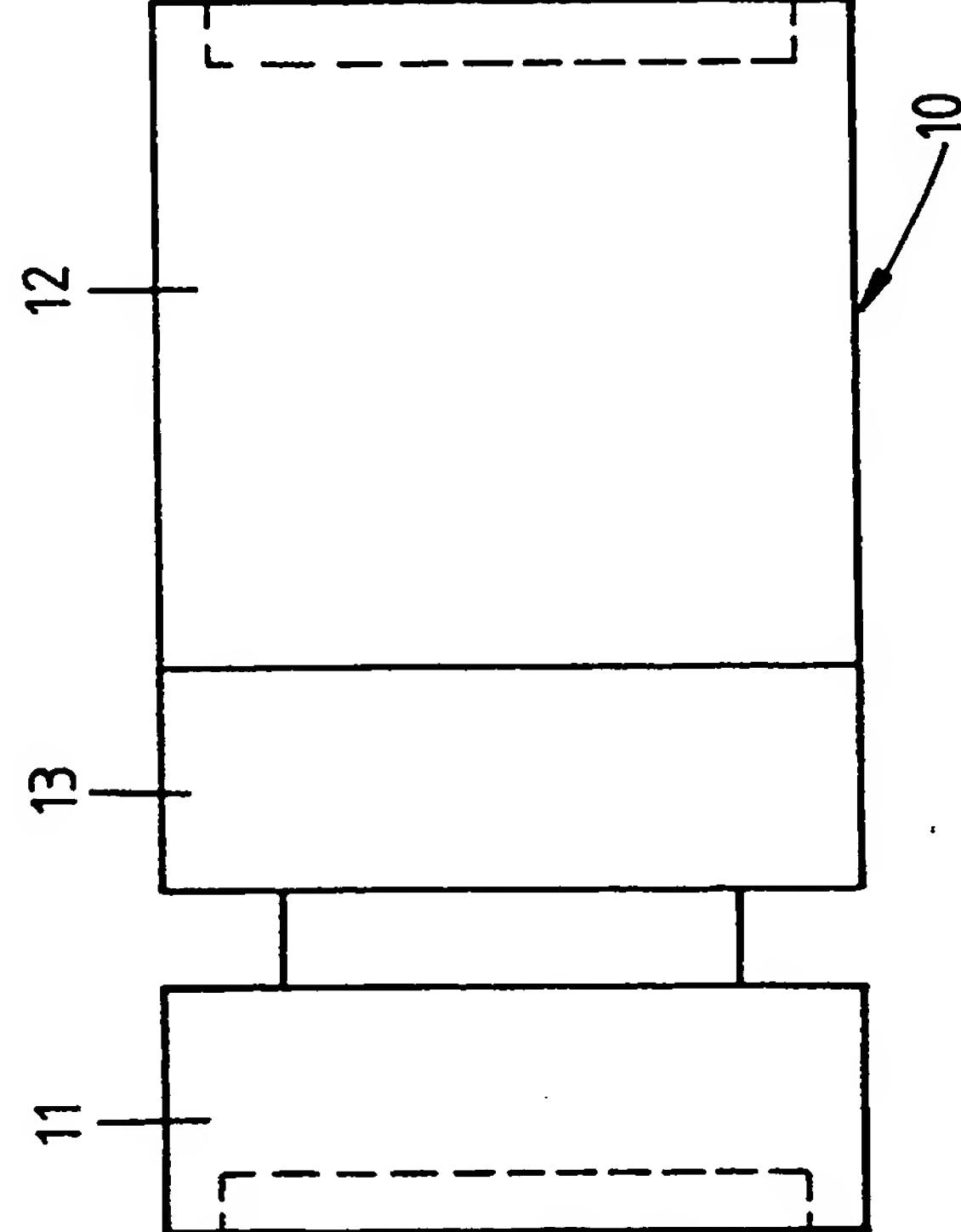


FIG 1G

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FIG 2bFIG 2cFIG 2aFIG 2d

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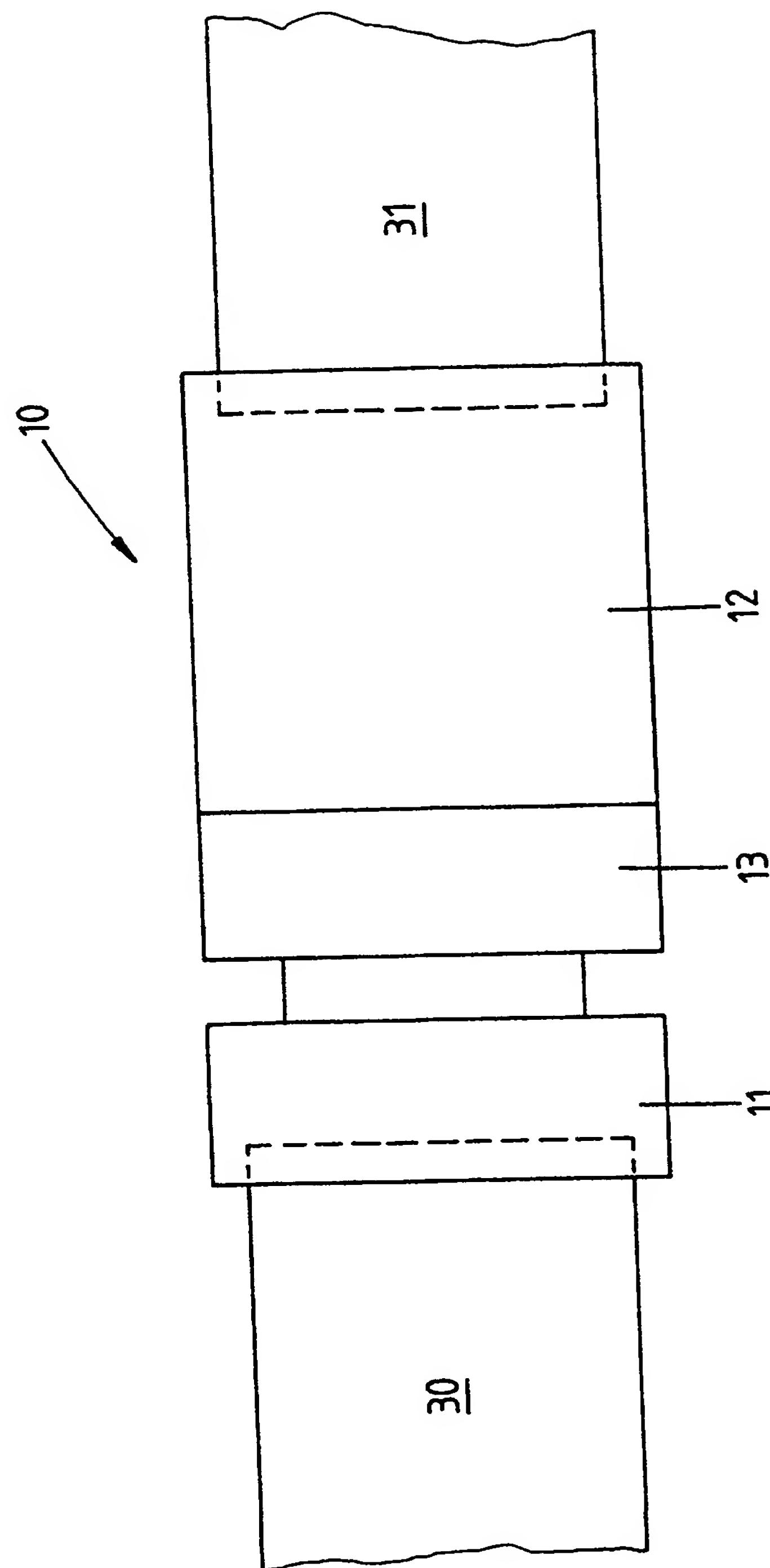


FIG 2e

**SUBSTITUTE SHEET (RULE 26)**

## INTERNATIONAL SEARCH REPORT

International Application No. <b>PCT/AU 98/00519</b>
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<b>A. CLASSIFICATION OF SUBJECT MATTER</b>																						
Int Cl <sup>6</sup> : A61L 27/00, 31/00																						
According to International Patent Classification (IPC) or to both national classification and IPC																						
<b>B. FIELDS SEARCHED</b>																						
Minimum documentation searched (classification system followed by classification symbols) IPC A61L 27/00, 31/00																						
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched AU: IPC as above																						
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) WPAT: (IPC and coral:) or (IPC and marine:) or (coral: and (surgic: or medic: or prosth: or bone: or implant:))																						
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>																						
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.																				
X	WO, 97/46178, (INTERPORE INTERNATIONAL) 11 December 1997 Whole document	1,5,7,11																				
X	WO, 97/31661, (LINDHOLM, T. Sam, et al.) 4 September 1997 Whole document	1,5,7,8,10																				
X	WO, 89/06944, (BESINS, Thierry, Rainer, et al.) 10 August 1989 Whole document	1,5,7																				
<input checked="" type="checkbox"/>	Further documents are listed in the continuation of Box C	<input type="checkbox"/> See patent family annex																				
<p>* Special categories of cited documents:</p> <table> <tr> <td>"A"</td> <td>document defining the general state of the art which is not considered to be of particular relevance</td> <td>"T"</td> <td>later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</td> </tr> <tr> <td>"E"</td> <td>earlier document but published on or after the international filing date</td> <td>"X"</td> <td>document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</td> </tr> <tr> <td>"L"</td> <td>document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</td> <td>"Y"</td> <td>document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</td> </tr> <tr> <td>"O"</td> <td>document referring to an oral disclosure, use, exhibition or other means</td> <td>"&amp;"</td> <td>document member of the same patent family</td> </tr> <tr> <td>"P"</td> <td>document published prior to the international filing date but later than the priority date claimed</td> <td></td> <td></td> </tr> </table>			"A"	document defining the general state of the art which is not considered to be of particular relevance	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention	"E"	earlier document but published on or after the international filing date	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone	"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art	"O"	document referring to an oral disclosure, use, exhibition or other means	"&"	document member of the same patent family	"P"	document published prior to the international filing date but later than the priority date claimed		
"A"	document defining the general state of the art which is not considered to be of particular relevance	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention																			
"E"	earlier document but published on or after the international filing date	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone																			
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art																			
"O"	document referring to an oral disclosure, use, exhibition or other means	"&"	document member of the same patent family																			
"P"	document published prior to the international filing date but later than the priority date claimed																					
Date of the actual completion of the international search		Date of mailing of the international search report <b>19 AUG 1998</b>																				
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No.: (02) 6285 3929		Authorized officer <b>J. TURNER</b> Telephone No.: (02) 6283 2071																				

## INTERNATIONAL SEARCH REPORT

International Application No. PCT/AU 98/00519
--

C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages  Whole document	Relevant to claim No.
X	WO, 87/07826, (CAMPRASSÉ, Serge, et al.) 30 December Whole document	1,5,6,7
X	Patent Abstracts of Japan, C-624, page 104, JP, 1-117833, (MASATOSHI KATO) 10 May 1989 Abstract	1,5
X	DE, 4130546, A1 (BAYLINK, David J. et al.) 18 March 1993 Whole document	1,5,7,8,10
X	US, 5563124, (DAMIEN et al.) 8 October 1996 Whole document	1,5,6,7,8,10
X	US, 5480827, (GUILLEMIN et al.) 2 January 1996 Whole document	1
X	US, 4976731, (PERRY) 11 December 1990 Whole document	1,5,7,11
X	EP, 532421, A1 (ITAC VAR-IMPLANT SARL) 17 March 1993 Column 1, lines 25-43	1,2,5,7
X	EP, 395187, (INTERPORE INTERNATIONAL) 31 October 1990 Whole document	1,2,5,6,7,8,9, 10,11
X	FR, 2637502, A1 (DUROSELLE, Patrick et al.) 13 April 1990 Whole document	1,5

**INTERNATIONAL SEARCH REPORT**  
Information on patent family members

International Application No.  
**PCT/AU 98/00519**

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report				Patent Family Member			
WO	9746178	AU	31521/97				
WO	9731661	AU	47216/96				
WO	8906944	AU	30462/89				
WO	8707826	BR	8707382	DK	905/88	EP	271548
		FR	2600246	MC	1855		
JP	11783336	GB	1203168	ES	361854	FR	1597275
		NL	6818612				
DE	4130546	AU	25539/92	EP	557498	US	5691305
		WO	9305823	US	5071655	DE	4130545
		AU	25841/92	EP	558727	WO	9305808
US	5563124	CA	2107481	EP	584283	US	5290763
		WO	9218142	US	5371191	EP	729325
		WO	9513767				
US	5480827	EP	549774	FR	2679250	WO	9302181
EP	532421	FR	2681235				
EP	395187	CA	2013420	EP	395187	JP	3068370
		US	4976736	ZA	9003187		
END OF ANNEX							

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